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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,766	DANGOND ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-46,49 and 52-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-46,49 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 25-46, 49, and 52-56, and a further election of the gene guanylate kinase (GUK1), in the reply filed on September 20, 2005 is acknowledged.

Claims 1-24, 44-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 20, 2005. It is noted that claims 44-46 and 49 are also withdrawn as they do not read on the elected invention. Claim 49 has been withdrawn because the Applicant has not elected a second gene product in Tables 16, 17, or 18 or CD 18.

It is noted that an additional election has been submitted September 29, 2005. While the serial number corresponds to the instant case, the Applicants' name, title of invention, Examiner, and election of invention do not appear to correspond to the instant invention. It appears that there was a typographical error regarding the serial number of the case and this election was not considered for the instant case.

Claims 25-46, 49, and 52-56 are under consideration.

Information Disclosure Statement

The information disclosure statement filed February 2, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document;

each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The IDS filed on February 2, 2004 is missing reference C5, Fernandez-Arquero et al., 1999. Because this reference was not provided, it was crossed off the IDS and it was not considered. All other art on the IDS of February 2, 2004 has been considered, as indicated by the Examiner's initials.

The information disclosure statement filed February 2, 2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it is missing a copy of reference C5, Fernandez-Arquero et al., 1999. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 25 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 46 of copending Application No. 10/430,762 ('762). Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are to methods of treating multiple sclerosis (MS) comprising administering to a subject with MS a drug/composition that causes a decrease in the level of a gene product. It is noted that the instant application also encompasses that the claimed invention prevents MS, which is not claimed matter in '762. While Applicant has selected GUK1 as the gene product to consider in the instant application, GUK1 is listed in table 1, page 11, of '762 as a gene product to be considered.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 25 of the instant application is directed to an invention not patentably distinct from claim 46 of commonly assigned '762. Specifically, both claims are drawn to methods of treating MS, comprising administering to a subject with MS a drug/composition that causes a decrease in the level of a gene product. It is noted that the instant application also encompasses that the claimed invention prevents MS, which is not claimed matter in '762. It is also noted that the Inventive Entities are different between the two Applications. The instant Application lists Dangond, Hwang, and Gullans as the Inventors; '762 lists Dangond and Hwang as the Inventors.

Claim 25 is provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 10/430,762 which has a common assignee and two common Inventors with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if published or patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future publication or patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131. This rejection might also be overcome by showing that the copending application is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-46, 49, and 52-56 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available

at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to a method for treating or preventing multiple sclerosis (MS) comprising administering to a subject with MS a composition that causes a decrease in the activity level or expression of guanylate kinase (GUK1). While the

claims have therapeutic implication, nothing in the specification provides any guidance that there is any relationship between GUK1 and MS.

In regards to the asserted utility, wherein method of treating or preventing MS is obtained by administering a composition that causes a decrease in the activity level or expression GUK1, the method does not constitute a real world utility and therefore is not a substantial utility, but rather represents further research on the product to identify or reasonably confirm a real world utility. As stated in the Guidelines set forth above, research that involves studying the properties of the claimed product itself does not constitute a substantial utility. Further, such an asserted utility constitutes a general, rather than a specific utility, generally there is utility for a method to treat or prevent a disease. Therefore, asserted utility 1) does not meet the standard for a specific and substantial utility.

In regards to asserted utility, wherein method of treating or preventing MS is obtained by administering a composition that causes a decrease in the activity level or expression GUK1, nothing in the specification teaches any composition that could be used to decrease the activity level or expression of GUK1. Further, nothing in the specification or art teaches that there is a relationship between GUK1 and MS such that reduction of GUK1 activity or expression would predictably result in treatment or prevention of MS. The specification generally discusses that the genes listed in the Tables were genes that were differenentially regulated in MS and non-MS patients. While there appears to be a difference between the kinds of genes that MS and non-MS patients express, nothing in the specification provides any guidance, especially with

GUK1, that GUK1 has any biological role in MS. (It should be pointed out at this moment that Table 3 indicates that GUK1 is downregulated in MS patients, not upregulated.) As it stands, because there is no known relationship between GUK1 and MS, an artisan might guess that GUK1 mRNA expression has gone down because the tissue that expresses it (e.g. glia) is destroyed during the course of the disease. In this case, GUK1 has no relationship with MS progression or initiation and as a result the specification fails to teach any specific, biological relationship associated with GUK1 and MS. Thus, in the absence of any specific teachings as to actual relationship between GUK1 and MS, the method of treating or preventing MS comprising administering to a subject with MS a composition that causes a decrease in activity level or expression of GUK1 is neither specific nor substantial as it would require further research to reasonably confirm role GUK1 has in the initiation or progression of MS.

Thus, in view of the discussion above, the skilled artisan would not find any of the asserted utilities of the claimed method to be specific and substantial, or well-established.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-46, 49, and 52-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention is drawn to a method for treating or preventing multiple sclerosis (MS) comprising administering to a subject with MS a composition that causes a decrease in activity level or express of guanylate kinse (GUK1). With regards to the invention being drawn to a method for preventing MS, the art at the time of filing and

post filing art teaches that there are no known ways to prevent MS. Compston and Coles, 2002, The Lancet, 359: 1221-1231 teach that, "current research is increasingly seen as coherent and focused on the hot topics that need to be solved to limit, repair, and prevent the damage caused by multiple sclerosis (Compston and Coles, page 1229, 2nd col., parag. under "The past and future of multiple sclerosis")" and the WebMD Health website (http://my.webmd.com/hw.multiple_sclerosis/hw191004.asp) teaches, "(g)enerally, there is no way to prevent multiple sclerosis (MS) or its attacks (WebMD Health website, 1st parag. under Multiple Sclerosis (MS) Prevention, see printout)." According to the art, part of the reason why the disease is hard to prevent is because MS is caused by an interplay between genes and the environment. The art teaches that "unlike some other complex traits, large Mendelian pedigrees do not seem to contaminate series and bias the evidence for heritability; multiple sclerosis seems to be genuinely polygenic." The art teaches that "the genes responsible for complex traits are not mutations coding for aberrant gene products but normal polymorphisms. They act independently or through epistasis, and each polymorphism can exert a small contributory effect on some as yet undefined structure or physiological function (Compston and Coles, page 1224, 2nd col., 1st and 2nd parags. under "What causes multiple sclerosis?")." The art teaches, however, that MS is not entirely a genetic disease. There appears to be an element of the environment as well. "In Austrailia and New Zealand, there are gradients in frequency that do not follow genetic clines. The risk is higher for English-speaking white people who migrate into South Africa as adults than as children. The low frequency of multiple sclerosis in Africans increases

substantially for first-generation descendants raised in the UK (Compston and Coles, page 1225, 1st col., 2nd parag.)." As the art provides no guidance, an artisan would look to the specification for guidance as to what steps one would need to perform in order to prevent MS. While the specification indicates that prevention is achieved by, "increasing in the level of a gene product selected from the group consisting of those genes indicated by a minus (-) sign in Tables 1-15, except those indicated by asterisk(s). In still yet a further embodiment, there is provided a method for ...preventing multiple sclerosis (MS) comprising administering to a subject with MS a composition that causes a decrease in the level of a gene product selected from the group consisting of those genes indicated by a plus (+) sign in Tables 1-15, except those indicated by asterisk(s) (specification, page 4, 1st parag.)," nothing in the specification teaches what compositions would need to be administered to decrease the activity of guanylate kinase (GUK1) and to prevent multiple sclerosis in a patient. Given that nothing in the art or the specification provide any guidance as to how to prevent MS, an artisan would need to undergo undue experimentation in order to obtain a composition that would prevent MS and reduce the activity or expression level of GUK1. Thus, neither the art nor the specification enables an artisan to prevent MS.

The claimed invention being drawn to a method of treating MS, comprising administering to a subject with MS a composition that causes a decrease in the activity level or expression of GUK1. While the art teaches that there are a few compounds that have been used in treating MS patients (e.g. see O'Connor, 2002, Neurology, 59 (Suppl. 3): S1-S33), nothing in the art teaches that these compounds decrease the

activity of GUK1. While not explicitly stated, it is inferred that the point of the invention is that therapy is achieved by changing the activity level or expression of GUK1 in an MS patient such that this change will result in treatment of MS or symptoms of MS (e.g. the specification indicates increasing the level of the gene product in patients that exhibit a gene indicated by a minus (-) sign in Tables 1-15, page 4, 1st parag.). As such, it is determined whether decreasing the activity level or expression of a GUK1 would result in any treatment of an MS patient. A search in the art indicates that there is no known treatment for increasing the expression level or activity of GUK1 and MS. Thus, the artisan would need to look to the specification for guidance. However, nothing in the specification provides any guidance for using any peptide, small molecule, organopharmaceutical, expression cassette comprising a nucleic acid encoding an antisense construct or ribozyme targeting the selected gene product operably linked to a promoter such that any of these peptide, small molecule, organopharmaceutical, expression cassette comprising a nucleic acid encoding an antisense construct or ribozyme targeting the selected gene product operably linked to a promoter decrease GUK1 gene expression or protein activity, wherein the composition is administered intradermally, subcutaneously, intramuscularly, intraperitoneally, intravenously, intranasally, intraalveolarly, parenterally, intrathecally, intraparenchymally, or intraperitoneally. An artisan would need to know what compound to use and how to administer a compound because the art teaches there is unpredictability in delivering a compound to the spinal cord. One big hurdle in delivering compound to the spinal cord

is that the drug needs to cross the blood brain barrier. Dietz and Bahr, 2004, Mol. Cell. Neurosci, 27: 85-131, teach that,

> "(o)n the one hand, drugs directed at intracellular target sites need to be sufficiently polar to be easily administered and well distributed in the organism. On the other hand, such substances also need to be hydrophobic enough to transverse the lipid bilayer of the cell. Thus, many drug leads fail to make it into clinical trials because they do not fulfill those physical properties. To circumvent problems of bioavailability, substances often need to be extensively modified or their formulation needs to be fine-tuned, for example, for substances that exhibit a low solubility in water. Such problems apply not only to chemically synthesized substances, but also to potentially therapeutic proteins as well. Cerebral drug delivery is faced with many additional obstacles due to the characteristics of the blood-brain barrier (BBB), in particular after trauma or stroke.
>
> Methods like electroporation, chemical transfection, or microinjection can be applied in vitro. However, they often damage the cells, and the mount of compound or protein delivered is not easily controlled (Dietz and Bahr, page 86, 2nd col. under "Delivery into cells and across the BBB—why Trojan horse trickery is in demand")."

As Dietz and Bahr's teaching indicates the unpredictability involved in modifying potential drugs such that the drug can be delivered and be available at appropriate amounts for treatment, nothing in the specification provides guidance to an artisan how to overcome these issues of unpredictability that it would require an artisan undue experimentation to obtain a drug such that it overcomes the problems in the art taught by Dietz and Bahr.

In addition to the issues addressed above by Dietz and Bahr, there is are also other issues of delivery that an artisan would need to know in order to appropriately delivery a composition that causes a decrease in activity or in the level of expression of GUK1. This issue focuses on determining which cells in the spinal cord should receive the composition that affects GUK1. The art generally teaches that GUK1 is an enzyme

that "catalyzes the reversible transfer of the terminal phosphoryl group of ATP to the acceptor molecule GMP (Konrad, 1992, JBC, 267: 25652-25655, abstract)." However, nothing in the art or specification provides any guidance that GUK1 has any biological relationship with MS. The artisan would need to know what relationship GUK1 has with MS because the art teaches that there are multiple events involving many different cell types that occur during the course of the disease (Compston and Coles, page 125-126, "Evolution of the plaque"). The art teaches that healthy individuals have autoreactive myelin T cells, normally kept in check by regulatory T cells. The breakdown in regulation is thought to be triggered by a peptide that is immunologically indistinguishable from self-antigen and subsequently, an appropriate response to infection generates inappropriate inflammation against some component of the oligodendrocyte-myelin unit. Like other organ-specific autoimmune diseases, this systemic defect results not in a sustained autoimmune attack on the entire target organ, but rather, in inflammatory lesions that are temporally and spatially segregated. The failure in regulation leads to proliferation, activation, and entry into the circulation of autoreactive T cells. T cells express adhesion molecules and induce changes in endothelia allowing access of T cells across the blood-brain barrier and into the central nervous system. The T cells then encounter antigen and activate microglia, which present antigen to the T cells, which in turn sets up a proinflammatory loop. When toxic inflammatory mediators are released, the breakdown of the blood-brain barrier is sustained and thus leads to injury of axons and glia. Nitric oxide which acts on normal or hypomyelinated axons, transiently blocks conduction and reversibly increases deficits

arising from already compromised pathways. As acute inflammation resolves, pathways are released from nitric oxide-induced physiological conduction block. Symptoms also improve as surviving functional pathways are reorganized at the cellular and systems level. While a patient may go into remission, his/her tissue is still vulnerable. When compounded with high axonal firing and nitric oxide, structural and irreversible changes occur to axons. Acute inflammatory plaques in patients reduce axons as the axons degenerate. Cytokines and growth-promoting factors released by astrocytes and microglia promote endogeous remyelination; however, astrocyte reactivity seals the lesion and gliosis causes a physical barrier to further remyelination. As such, most axonal loss is seen in secondary progressive multiple sclerosis. It is thought that axonopathy does not appear to be due directly to inflammaltion, but results from loss of trophic support normally provided to axons by myelin or glia, acting directly or through the maintenance of electrical activity or both. As the art teaches that the disease is comprised of different cell types and different phases, some of which the damage from the disease is permanent, and as neither the art nor the specification provide guidance as to what relationship there is between GUK1 and MS, an artisan does not know a where and when a compound affecting GUK1 protein or gene product should be administered. While it may be that GUK1 could have a role in MS, it also may not. It should be pointed out at this moment that GUK1 is a gene that is downregulated in MS patients (specification, Table 3, page 19) and is contrary to the method as claimed in claim 25, which is to a method of reducing genes that are upregulated in MS patients. The decrease in GUK1 expression could result from the

fact that GUK1 is expressed in glia and death of glia in the disease results in decrease of GUK1 expression. As such, even if a compound were administered to glia to increase the level of GUK1 expression or increase activity of GUK1, nothing in the specification provides guidance that increasing GUK1 in glia has therapeutic effects in MS. The bottom line of the instant issue is that because it is not clear what biological relationship GUK1 has with MS, an artisan cannot predictably arrive at the claimed invention. As such, given that the art teaches the complexity of the disease as it involves many different cell types and results in tissue damage, which is irreversible and any mechanisms of repair are unknown, an artisan would require undue experimentation in order to be enabled for any method of treating MS using any composition comprising any peptide, small molecule, an oragnopharmaceutical, or any nucleic acid encoding an antisense construct or ribozyme, wherein the composition is administered intradermally, subcutaneously, intramuscularly, intraperitonealy, intravenously, intranasally, intraalveolarly, parenterally, intrathecally, intraparenchymally, or intraperitoneally, and wherein the composition affects any cell.

In addition to the above issues, further issues of enablement are drawn to issues of gene therapy. Particular attention is drawn to the issue that the claimed invention also encompasses the embodiment that the composition comprises an expression cassette comprising a nucleic acid sequence encoding an antisense construct or a ribozyme targeting the selected gene product, wherein the nucleic acid sequence is operably linked to any promoter, given that an artisan does not know what cells should be targeted to administer GUK1 antisense or ribozyme, an artisan would not know what

kind of promoter should be used to target GUK1 expression, given that it is not completely clear which cells should be expressing GUK1 antisense or ribozyme. With regards to the choice of vector as a vehicle, the art teaches unpredictability in using vectors in gene therapy. One problem associated with using non-viral DNA vectors is that they suffer from inefficient gene transfer. Abdallah et al. 1995, Biol. Cell., 85: 1-7 teach that one of the major hurdles in using non-viral DNA *in vivo* is successfully having the vector enter the nucleus (Abdallah, et al., page 2, 1st col., 2nd parag.). In addition to this, expression from these non-viral vectors is transient (Somia and Verma, 2000, Nature Reviews, 1:91-99; page 91, 1st col., 2nd parag., lines 2-8)). With regards to using viral vector, the art teaches some viral vectors are not enabled for certain applications. For example, a retroviral vector is not able to infect non-dividing cells, such as brain (Somia and Verma, page 92, 2nd col., 3rd parag). In the case of adenoviral vectors, the art teaches that one major problem with using them is that they are destroyed by the host's immune system shortly after they are introduced to the host. Cellular immunity eliminates the transduced cells, whereas humoral immunity precludes the repeat administration (Somia and Verma, page 95, 1st col., 1st parag.). In light of these teachings in the art, a skilled artisan would need to determine if long-term or short-term of gene expression is required for his/her study, determine whether or not the means of introducing a non-viral DNA expression vector is sufficient for duration of the study and whether the transgene is expressed at levels that have therapeutic effect. In other words, gene therapy may not be a salient system to use for gene expression. For

reasons of unpredictability and undue experimentation, the specification has not enabled a skilled artisan to reliably use gene therapy as a method for treating MS.

Thus, in light of the above teachings, it follows that an artisan is not enabled for the claimed method and for the further embodiments of:

wherein the method further comprises a second MS therapy and

wherein the composition is administered more than once or in repeated discrete dosings. It is noted that given the unpredictability in the art and the lack of teachings in the specification to overcome these issues of unpredictability, an artisan could not practice the claimed invention and would not be able to practice the claimed inventions for its further embodiments such as steps including other MS therapies and repeat administration.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-46, 49, and 52-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 is drawn to a method of treating or preventing MS comprising administering to a subject with MS a composition that causes a decrease in the activity level or expression of GUK1 (wherein

GUK1 is selected from the group consisting of those gene indicated by a plus (+) sign in Tables 1-15, other than those indicated by an asterisk). However, according to Table 3, GUK1 is indicated by a minus (-) sign. At the moment, the selection of GUK1 for examination appears contrary to the context claim 25. Claims 26-46, 49, and 52-56 depend on claim 26.

Claims 52 recite the limitation "said neuronal cell" in claim 49. There is insufficient antecedent basis for this limitation in the claim.

Claim 53 recites the limitation "said glial cell" in claim 49. There is insufficient antecedent basis for this limitation in the claim.

Claim 54 recites the limitation "said intravascular cell" in claim 49. There is insufficient antecedent basis for this limitation in the claim.

Claim 55 recites the limitation "said perivascular cell" in claim 49. There is insufficient antecedent basis for this limitation in the claim.

Claim 56 recites the limitation "said central nervous system-infiltrating immune cell" in claim 49. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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